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Sustained Release Bi-Layered Tablets of Diltiazem Hydrochloride Using Insoluble Matrix System

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A study was undertaken to formulate sustained release tablets by utilizing the bi-layer concept. The formulation contained a fast release layer and a sustaining layer. Ethylcellulose and rosin were used as the matrix forming materials. Matrix tablets of diltiazem hydrochloride were formulated using ethylcellulose or rosin as matrix materials in various quantities (%w/w) to study their ability to retard the release and were evaluated for hardness, friability and drug release. *In vitro* release from the formulation was studied as per the USP XXIII dissolution procedure. The formulations gave an initial burst effect followed by sustained release for 12 h which indicates bimodal release of diltiazem HCl from the matrix tablets. The data obtained were fitted into Higuchi's models. Analysis of *n* values of Korsmeyer equation indicated that the drug release involved both diffusional and dissolutional mechanisms.

Diltiazem hydrochloride, an orally active calcium channel blocking agent, is used in the treatment of angina pectoris, hypertension and arrhythmia[1-2]. It is highly water soluble drug, and is rapidly and almost completely (60-70%) absorbed from GIT, following oral administration, but undergoes extensive hepatic metabolism. The biological half-life of the drug is 3.5±1.2 h[3]. It is typically administered three or four times daily, in the form of conventional tablets. Thus frequent administration leads to a constant change in the blood concentration. To overcome the frequent administration and to minimize the peak-to-trough oscillation of the blood concentration, sustained release formulations are developed.

Multilayered tablet concept has long been utilized to develop sustained release formulation. Such a tablet has a fast releasing layer and may contain one (bi-layered) or two (triple) layers, to sustain the drug release[4]. The pharmacokinetic advantage relies on the criterion that, drug release from the fast releasing layer leads to a sudden rise in the blood concentration. However the blood level is maintained at steady state, as the drug is released from the sustaining layer.

Rosin is an oleoresin residue left after distilling the volatile oil from various species of pinus (Fam: Pinaceae). The principle constituent of rosin is abietic acid. Rosin used in pharmacy occurs as sharply angular, amber coloured glassy material[5]. Rosin derivatives and modified rosin have been utilized as anhydrous binding agents[6]. Matrix tablets of diabietic acid, a derivative of abietic acid, extracted from rosin were studied as retardant material[7] and it was concluded as matrix material for prolong release formulations of water soluble drugs. Maleic adducts of rosin has been successfully tested as matrix oral sustained release formulations[8]. The present study aims at formulating bi-layered tablets of diltiazem hydrochloride, with a fast release layer and a sustaining layer. The study involves utilization of rosin and ethylcellulose as insoluble matrix materials in sustaining layer.

MATERIALS AND METHODS

Diltiazem hydrochloride was obtained as a gift sample

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from Sain Medicaments, Hyderabad. Ethylcellulose (15 centipoise) was procured from Robert Johnson, Germany. Rosin was locally procured. Starch was obtained from Meghana Products, Mumbai. Talc was procured from Swastik Pharmaceuticals, Mumbai. Magnesium stearate was procured from Nice Chemicals, Nagpur. Lactose IP was procured from Genuine Chemicals, Mumbai. All the materials were used as received. Rosin is a water insoluble resin. But it is soluble in organic solvents such as acetone and chloroform. Rosin gives emerald green florescence on shaking with light petroleum ether and then treating this layer with dilute copper acetate solution[5]. The acid value of rosin was determined using the method reported in IP (1995)[9].

Preparation of matrix tablets:

The matrix tablets were prepared by wet granulation. The drug, polymers and other excipients used were passed through sieve No. 80 before their use in the formulation. The layer with sustaining dose was formulated with various amounts of polymer. The dose in the formulation for fast release was 30 mg. The maintenance dose or sustaining dose of diltiazem hydrochloride was calculated as per reported method[10].

Formulation of fast release layer:

The fast release layer was formulated by mixing diltiazem hydrochloride, uniformly with starch and lactose by following the formulae as per Table 1. Granulation was carried out by wet granulation method by adding sufficient quantity of alcohol. The granules were mixed with talcd and magnesium stearate.

Formulation of sustaining layer:

Granules for sustaining layer were prepared by mixing maintenance dose of diltiazem hydrochloride, with matrix materials[11] (ethylcellulose or rosin), following the formulae given in Table 2. The powders were granulated using sufficient quantity of acetone till a wet mass was formed. The cohesive mass obtained was passed through sieve no.16 and the granules were air dried at room temperature for 6 h. The dried granules were again sieved by passing through sieve No.22. The granules were mixed with talc and magnesium stearate. The required amount of granules for fast release layer was compressed lightly using a single station tabletting machine (Cadmach Machinery Co. Pvt. Ltd., Mumbai) using 8 mm round and flat punches. Over this compressed layer, required quantity of the granules prepared for sustaining layer was placed and compressed with maximum force to form a bi-layered tablet.

Evaluation of the formulation:

Flow properties of the prepared granules were evaluated. Other properties of the granules evaluated were bulk density, true density, apparent density, and porosity using standard reported methods[12]. Hardness and friability of the tablets formulated were evaluated using a Monsanto hardness tester and a Roche friabilater, respectively.

Drug content:

The prepared tablets were analyzed for diltiazem hydrochloride content. Tablets were crushed into a fine powder and diltiazem hydrochloride was extracted into water by shaking the crushed powder with water mechanically for 2 h. The supernatant liquid was filtered, diluted suitably and estimated in a double beam UV-spectrophotometer (UV-240, Shimadzu, Japan) at λmax 237 nm.

***In vitro* drug release study[13]:**

Release of diltiazem was determined using a six panel, USP XXIII dissolution apparatus-2 (Tab Machines, Mumbai) at 100 rpm. The dissolution was studied using 900 ml of phosphate buffer saline (pH 7.4). The temperature was maintained at 37±2°. Samples of 5 ml each were withdrawn at appropriate time intervals throughout the dissolution study of 12 h for analysis. Each sample withdrawn was replaced with an equal amount of fresh dissolution medium. Samples were suitably diluted and analysed for diltiazem hydrochloride content using a double beam UV-spectrophotometer (UV-240, Shimadzu, Japan) at λmax 237 nm.

The rate and the mechanism of release of diltiazem hydrochloride from the prepared matrix tablets were analysed by fitting the dissolution data into[14], zero-order equation, $Q=Q_o-k_o t$ (1), where Q is the amount of drug released at time t, and k_o is the release rate. first order equation, $\ln Q=\ln Q_o - k_1 t$ (2), where k_1 is the release rate constant and Higuchi's equation, $Q=k_2 t^{1/2}$ (3), where Q is the amount of drug released at time t and k_2 is the diffusion rate constant. The dissolution data was further analyzed to define the mechanism of release by applying the dissolution data following the empirical equation, $M_t/M\alpha=Kt^n$ (4), where $M_t/M\alpha$ is the fraction of drug released at time t. K is a constant and *n* characterizes the mechanism of drug release from the formulations during dissolution process.

RESULTS AND DISCUSSION

Over the last few years a large number of naturally obtained gums were evaluated as release retardants. Since they are of natural origin they are non-toxic, biocompatible

and cheaper. Rosin, a naturally obtained insoluble resin along with ethylcellulose, which is a hydrophobic matrix forming material with proven ability to retard the drug release were utilized in this study. Rosin when powdered was of yellowish colour. The particles were of irregular shape when examined under compound microscope. Formation of emerald green florescence with petroleum ether layer confirms the sample is of rosin. The emerald green colour is due to formation of copper salt of abietic acid. The acid value of rosin was determined as 162±1.2 as against a standard value of 150-180[5].

The prepared granules were evaluated for various physical properties as reported earlier. The bulk densities for the granules of various formulations ranged between 0.91±0.13 g/cc to 2.11±0.54 g/cc as determined by tap method. This value of bulk density indicates of good packing character. The compressibility index (I) for all the formulations was found to be below 15%, indicating desirable flow properties, as the 'I' value below 15% indicates good flow properties. The flow property of granules was further analysed by determining static angle of repose. The angle of repose values for all the granules ranged between 24.3±0.92° to 30.1±2.78°. This value indicates good flow property of the granules with ethylcellulose or rosin as matrix material, since lower the angle of repose, better is the flowability.

The composition of immediate release layer of matrix tablet as shown in Table 1 is constant for all the formulations. However the composition of sustaining layer (Table 2) differs only in drug to matrix material (rosin or ethylcellulose) ratio. The matrix tablets were of round shape and flat with a diameter of 8 mm. The hardness of tablets ranged from 4-5.5 kg/cm^2. The percentage friability of all the formulations was between 0.83±0.12 % to 1.32±0.19 %. The values of hardness test and percent friability indicate good handling property of the prepared bi-layered tablets. The drug content of the formulations was uniform (>95 %) in all the cases.

The release of diltiazem hydrochloride from the prepared formulations was analysed by plotting the cumulative percent drug released vs time (h) as shown in fig. 1. Simple visual observation of the plot shows an initial burst effect. From all formulations, over 30% of the diltiazem HCl was released within the first hour of dissolution study. This initial high amount of diltiazem HCl release can be attributed to release of drug from immediate release layer of the formulations. However, further release of diltiazem hydrochloride from the formulations was sustained for 12 h. The initial release of diltiazem HCl with MT1 (44.7±2.23 %) and MT4 (52.7±3.51 %) was very high compared to other formulations. This high percent release is due to diltiazem HCl

TABLE 1: FAST RELEASE LAYER OF THE FORMULATION

Ingredients	Quantity for single Tablet (% w/w)
Diltiazem hydrochloride	41
Starch powder	28
Lactose I.P	28
Talc powder	1
Magnesium stearate	2

The fast release layer was prepared by mixing diltiazem hydrochloride, starch and lactose uniformly. The powder was granulated by adding alcohol drop wise. The granules prepared were air dried and mixed with talc and magnesium stearate.

TABLE 2: SUSTAINING LAYER OF THE FORMULATION

Ingredients (% w/w)	MT- 1	MT- 2	MT- 3	MT-4	MT- 5	MT- 6
Diltiazem HCl	63.64	48.63	38.73	63.64	48.63	38.73
Ethylcellulose	32.58	48.63	57.52	--	--	--
Rosin	--	--	--	32.58	48.63	57.52
Talc	1	1	1	1	1	1
Magnesium stearate	2	2	2	2	2	2

The sustaining layer was prepared by mixing Diltiazem hydrochloride and the polymer in different amounts uniformly. The powder was granulated by adding acetone drop wise. The granules prepared were air dried and mixed with talc and magnesium stearate.

TABLE 3: ANALYSIS OF RELEASE MECHANISM OF DILTIAZEM HCL

Formulation	Zero order	First order	Higuchi Eqn. (r^2)	n value
MT1	0.7091	0.7690	0.9023	0.6261
MT2	0.8109	0.7995	0.9271	0 6192
MT3	0.8277	0.7862	0.8624	0.6158
MT4	0.8269	0.6774	0.981	0.6265
MT5	0.9487	0.861	0.9912	0.631
MT6	0.8832	0.7973	0.8916	0.6063

The dissolution data was fitted into zero order equation (1), first order equation (2), Higuchi model (3) and Korsmeyer model (4).

release from immediate release layer and also release of drug from the surface of sustaining layer of the tablet. However at the end of 12 h dissolution study, the cumulative percent release of diltiazem HCl was 85.8±3.30 (MT1) and 86.2±4.67 (MT4). Although there is a difference with cumulative percent drug released within the first hour of dissolution test, at the end of 12 h dissolution test the difference in drug release was negligible. The order of formulations according to diltiazem HCl release is MT4>MT1>MT5>MT2> MT3>MT6. The release of dilatiazem HCl from the matrix material (rosin or ethylcellulose) decreases with increase in the matrix content. Hence by changing the content of matrix material desired release rate can be obtained.

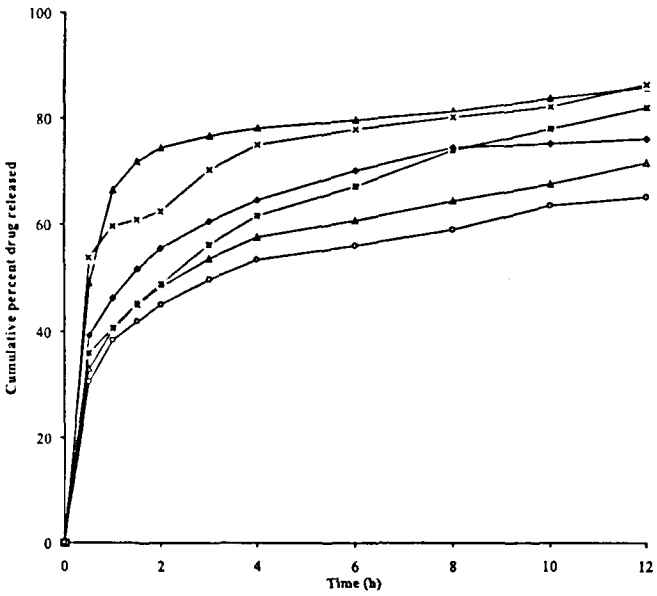

Fig. 1: Diltiazem HCl release profile from the matrix tablets.

***In vitro* drug release study was carried out according to USP XXIII, using apparatus-2, at 100 rpm on matrix tablets MT1(-▲-), MT2(-◆-), MT3(-△-), MT4(-x-), MT5(-✳-), and MT6(-◇-) using PBS (pH 7.4) as the dissolution medium. Samples drawn at regular intervals were analyzed for the drug content using double beam UV spectrophotometer at 237nm.**

The experimentally measured amount of drug released was plotted vs square root of time. In every case, the release of drug from the matrix tablets follows a pattern clearly in accordance with $t^{1/2}$ model of Higuchi[15]. The analysis of the regression value (Table 3) indicated that mechanism of drug release was primarily by diffusion. Values of *n* of the empirical equation (4) for all the formulations (>0.43<0.89) shows a combination of diffusional and dissolutional release mechanism[16], indicating the drug release from the formulations is controlled by more than one process.

REFERENCES

1. Cutler, N.R. and Archer, S., **J. Clin. Pharmacol.**, 1995, 35, 189.
2. Nicaise, J. and Neveux, E., **J. Int. Med. Res.**, 1995, 23, 244.
3. Echizen, H. and Eichelbaum, M., **Clin. Pharmacokinet.**, 1986, 11, 425.
4. Swintosky, J., **US Patent No.**, 2951792, 1960.
5. Evans,W.C., Eds., In; Trease and Evan's Pharmacognosy, 13th Edn., ELBS, London., 1989, 441.
6. Pathak, Y.V. and Dorle, A.K., **Eastern Pharmacist**, 1985, 131.
7. Ramani, C.C.. Puranik, and Dorle, A.K., **Int. J. Pharm.**, 1996, 137, 11.
8. Lalla, J.K., Karnik, S.S. and. Karnik, V.C., **Indian Drugs**, 1993, 30, 405.
9. Indian Pharmacopoeia, 4th Edn., Ministry of Health & Family welfare, New Delhi., 1995, A-50.
10. Rawlins, E.A., Eds., In; Bentley's Text Book of Pharmaceutics, 8th Edn., ELBS, London, 1977, 663.

11. Krishnaiah, Y.S.R. and Patro, S.S., **Pharma times,** 2001, 33, 16.
12. Lieberman, H.A., Lachman, L and Schwartz, J.B., Eds., In: Pharmaceutical Dosage Forms: Tablets, Vol. 2, Marcel Dekker, Inc, New York, 1981, 186.
13. United States Pharmacopoeia., 23rd Edn., United States Pharmacopoeia Convention, Inc., Rockville, MD, 1995, 1791.
14. Salomon, C.J., Bravo, S.A. and Lamas, M.A., **J. Pharm. Pharm. Sci.,** 2002, 5, 213.
15. Higuchi, T., **J. Pharm. Sci,** 1963, 52, 1145.
16. Catellani, P., Vaona, G., Plazi, P. and Colombo, P., **Acta Pharm. Technol.,** 1988, 34, 38.